

Efficacy of combined cataract extraction and endoscopic cyclophotocoagulation for the reduction of intraocular pressure and medication burden

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Received: 2015-08-03 Accepted: 2015-09-25

Abstract

• **AIM:** To report on the efficacy of combined endoscopic cyclophotocoagulation (ECP) and phacoemulsification cataract extraction (PCE) with intraocular lens placement for reduction of intraocular pressure (IOP) and medication burden in glaucoma.

• **METHODS:** A retrospective case review of 91 eyes (73 patients) with glaucoma and cataract that underwent combined PCE/ECP surgery was performed. Baseline demographic and ocular characteristics were recorded, as well as intraocular pressure, number of glaucoma medications, and visual acuity postoperatively with 12-month follow-up. Treatment failure was defined as less than 20% reduction in IOP from baseline on two consecutive visits (at 1, 3, 6, or 12mo postoperatively), IOP ≥ 21 mm Hg or ≤ 5 mm Hg on two consecutive visits, or additional glaucoma surgery performed within 12mo after PCE/ECP.

• **RESULTS:** Overall, mean medicated IOP was reduced from 16.65 mm Hg at baseline to 13.38 mm Hg at 12mo ($P < 0.0001$). Mean number of glaucoma medications was reduced from 1.88 medications at baseline to 1.48 medications at 12mo ($P = 0.0003$). At 3mo postoperatively, the success rate was 73.6% (95%CI: 63.3, 81.5), 57.1% at 6mo (95% CI: 46.3, 66.6), and 49.7% at 12mo (95%CI: 38.9, 59.6). Patient demographic characteristics were not associated with treatment success. The only ocular characteristic associated with treatment success was a higher baseline IOP.

• **CONCLUSION:** Combined PCE/ECP surgery is an effective surgical option for the reduction of IOP and medication burden in glaucoma patients. Patients with

higher baseline IOP levels are most likely to benefit from this procedure.

• **KEYWORDS:** endoscopic cyclophotocoagulation; glaucoma; cataract extraction

DOI:10.18240/ijo.2016.05.09

Roberts SJ, Mulvahill M, SooHoo JR, Pantcheva MB, Kahook MY, Seibold LK. Efficacy of combined cataract extraction and endoscopic cyclophotocoagulation for the reduction of intraocular pressure and medication burden. *Int J Ophthalmol* 2016;9(5):693-698

INTRODUCTION

Although lowering intraocular pressure (IOP) has remained the goal of glaucoma treatment, the refinement of established techniques and the emergence of new technologies have led to the rise of novel procedures to achieve this aim. Endoscopic cyclophotocoagulation (ECP) represents one such procedure that incorporates the established technique of diode laser cyclophotocoagulation (CPC) with an ab interno approach enabled by endoscopy. The advantage of such an approach is that direct visualization of the ciliary body permits targeted ablation and decreases the considerable risk of complications associated with the imprecise trans-scleral approach^[1]. While trans-scleral CPC has been reserved for refractory glaucoma or eyes with limited vision potential, the indications for ECP are much broader and include the treatment of mild to severe glaucoma of many types in patients of all ages^[2].

ECP (Beaver-Visitec Endo Optiks, Waltham, MA, USA) is performed with the use of an 18-23 gauge probe equipped with an 810 nm diode laser, 175-watt xenon light source, a helium-neon aiming beam, and video imaging all integrated through a fiber optic cable. It can be performed as a stand-alone procedure or combined with cataract extraction. Combining ECP with phacoemulsification cataract extraction (PCE) in a single procedure is attractive for several reasons. First, the small incision, clear-corneal approach used for modern phacoemulsification is easily compatible with the ECP instrumentation. Second, ECP is optimally performed in aphakic or pseudophakic patients^[3]. Finally, due to the frequent coexistence of these two age-related eye diseases, many patients are candidates for both procedures to achieve improved vision and IOP control^[4-5].

The efficacy and safety of ECP alone have been demonstrated [2,6]. Several recent studies investigating combined PCE/ECP demonstrate decreased IOP and medication burden with varying rates of treatment success^[7-11]. The aim of this study, therefore, was to further characterize the efficacy of PCE/ECP in the reduction of IOP and glaucoma medication burden in patients with a variety of glaucoma diagnoses with 12mo follow-up.

SUBJECTS AND METHODS

After approval from the Colorado Multiple Institutional Review Board was obtained, a retrospective review was conducted examining the medical records of patients who underwent PCE/ECP surgery at the University of Colorado outpatient surgery center between January 1, 2007 and July 31, 2013. Because of the retrospective nature of this review, no informed consent was required. Inclusion criteria for analysis included 1) age under 85y at the time of surgery and 2) sufficient follow-up, defined as attending at least 2 of the follow-up visits at 1, 3, 6, and 12mo. Exclusion criteria included 1) any patient under 40y or older than 85y and 2) patients undergoing an additional glaucoma procedure at the time of PCE/ECP.

Indications for surgery included the presence of visually significant cataract and uncontrolled IOP, glaucoma medication intolerance, and desire for decreased medication dependence. The surgical procedure was performed similarly by one of three surgeons (Seibold LK, Pantcheva MB and Kahook MY). All procedures were performed using topical and intracameral anesthesia. Additional anesthesia was delivered using 2% lidocaine and 0.75% bupivacaine to the sub-Tenon's space at the discretion of the surgeon for pain not controlled with the topical regimen. The cataract extraction was performed first using a traditional divide and conquer phacoemulsification technique through a 2.4 mm clear corneal incision. After placement of the intraocular lens, the sulcus was deepened with a cohesive viscoelastic to facilitate access to the ciliary processes. The endoscope was connected to the laser console and the laser was set to a power of 0.25 W and continuous duration. The endoscopic image was focused and oriented on the screen before application of the laser. The endoscope was introduced through the main incision and positioned near the ciliary processes until an average of 5-7 processes were visualized on screen. CPC of the nasal 200-270 degrees of ciliary body was performed in a continuous fashion. The treatment endpoint was contraction and whitening of the processes with care taken to avoid rupture of any ciliary processes. The degree of ciliary body ablation was determined by the extent of visualization through a single incision and surgeon discretion. After endoscope removal, the remaining viscoelastic was removed from the capsular bag, sulcus, and anterior chamber using irrigation and aspiration. All wounds

were then hydrated and checked to ensure a water-tight closure. Postoperatively, patients received a standard postoperative regimen for cataract surgery including topical moxifloxacin 0.5% (Vigamox, Alcon, Ft. Worth, TX, USA), prednisolone acetate 1% suspension, and a topical non-steroidal anti-inflammatory drug (NSAID) dosed four times per day for one week. The moxifloxacin was discontinued after one week, and the prednisolone and topical NSAID tapered over 4-6wk based on the level of intraocular inflammation. Glaucoma medications were restarted according to surgeon discretion.

Baseline demographic and ocular data were gathered, along with postoperative data from follow-up visits at 1, 3, 6, and 12mo. The number of glaucoma medications was recorded based on the number of prescribed glaucoma medications the patient was using at the beginning of each visit. All visual acuity (VA) values were converted from Snellen notation to logMAR values using criteria set forth by Shaarawy *et al*^[12] and Holladay^[13].

Criteria for treatment failure were modified from failure criteria used in the Tube Versus Trabeculectomy Study^[14] and defined as any of the following:

- 1) Less than a 20% reduction in IOP at two consecutive follow-up visits beginning at the 1-month visit.
- 2) IOP ≥ 21 or ≤ 5 mm Hg at two consecutive follow-up visits beginning at the 1-month visit.
- 3) Subject requires additional glaucoma surgery within 12mo of undergoing PCE/ECP.

Descriptive statistics were produced, including a Kaplan-Meier plot, and associations with treatment failure were assessed using t -tests and χ^2 or Fisher's exact tests. To assess longitudinal change in IOP from baseline, general linear mixed models accounting for within-patient correlation and adjusted for number of medications were used. IOP was log-transformed and results are presented as geometric means on the original IOP scale (mm Hg)^[15]. Tests for pairwise comparisons in these models were adjusted using Tukey's method. To assess change from baseline in medication count and VA, Wilcoxon signed rank tests were used due to notable non-normality; median and percentile values are reported accordingly. Secondary sensitivity analyses, using paired t -tests and relying on the central limit theorem to provide robustness against incorrect model assumptions, were conducted to evaluate changes in the more commonly reported mean values, with congruent results between the two tests supporting the hypothesis that there was significant change from baseline. All hypothesis tests are two-sided and the *a priori* significance level was set at 0.05.

Data preparation and descriptives were produced using R version 3.2.0 (2015-04-16)^[16]. The Kaplan-Meier analysis was conducted using the KMSurv package for R^[17]. All figures were created using the ggplot2 package for R^[18]. Longitudinal models were fit using version 9.4 of the

Table 1 Baseline demographic and ocular characteristics for eyes by surgery success or failure

Characteristic	Overall		Success		Failure		P
	Count or mean	% or SD	Count or mean	% or SD	Count or mean	% or SD	
Gender (n=91)							
M	43	47.3	19	41.3	24	53.3	0.3476
F	48	52.7	27	58.7	21	46.7	
Age (n=91)	70.91	9.40	70.54	9.27	71.29	9.63	0.7077
Ethnicity/race (n=91)							
Non-hispanic, Asian	9	9.9	3	6.5	6	13.3	0.2100
Non-hispanic, Black	13	14.3	9	19.6	4	8.9	
Non-hispanic, White	42	46.2	18	39.1	24	53.3	
Other	27	29.7	16	34.8	11	24.4	
Prior glaucoma surgery (n=91)							
No	48	52.7	23	50.0	25	55.6	0.7484
Yes	43	47.3	23	50.0	20	44.4	
Prior surgery type (n=43)							
Incisional glaucoma surgery	13	30.2	6	26.1	7	35.0	0.6501
Laser iridotomy	11	25.6	8	34.8	3	15.0	
Laser iridotomy, incisional glaucoma surgery	2	4.7	1	4.3	1	5.0	
Laser trabeculoplasty	13	30.2	6	26.1	7	35.0	
Laser trabeculoplasty, incisional glaucoma surgery	3	7.0	1	4.3	2	10.0	
Other laser	1	2.3	1	4.3	0	0.0	
Diagnosis (n=91)							
POAG	59	64.8	27	58.7	32	71.1	0.2940
PDG	2	2.2	1	2.2	1	2.2	
PXG	4	4.4	3	6.5	1	2.2	
CACG	12	13.2	9	19.6	3	6.7	
Other	14	15.4	6	13.0	8	17.8	
Baseline medication count (n=91)	1.88	1.07	1.78	1.09	1.98	1.06	0.3886
Baseline BCVA (n=88)	0.54	0.60	0.57	0.68	0.51	0.50	0.6651
Baseline IOP (n=91)	17.20	6.07	19.85	6.87	14.49	3.49	<0.0001

Counts and column percentages are shown for categorical data, means and standard deviations for continuous data. SD: Standard deviation; POAG: Primary open angle glaucoma; PDG: Pigment dispersion glaucoma; PXG: Pseudoexfoliative glaucoma; CACG: Chronic angle closure glaucoma; BCVA: Best corrected visual acuity.

SAS/STAT™ software suite (SAS Institute Inc., Cary, NC, USA) for Unix.

RESULTS

Of the 100 subjects (123 eyes) that underwent PCE/ECP surgery during the defined period, 73 subjects (91 eyes) were included in the final analysis based on the inclusion criteria outlined above. The most common indication for combining ECP with PCE surgery was uncontrolled IOP (n=74), followed by glaucoma medication intolerance (n=10) and desire for decreased medication dependence (n=7). The most common diagnosis was primary open angle glaucoma (n=59); other diagnoses included chronic, subacute, and acute angle closure glaucoma (n=14), normal tension glaucoma (n=7), secondary glaucoma (n=5), pseudoexfoliative

glaucoma (n=4), and pigmentary glaucoma (n=2). Additional baseline ocular and demographic characteristics are presented in Table 1. Only baseline IOP was associated with surgery success or failure, with a higher baseline IOP associated with surgery success (P<0.0001).

Success Survival The success rate at 3mo was 73.6% (95% CI: 63.3, 81.5; n=67); at 6mo, 57.1% (95%CI: 46.3, 66.6; n=52); and at 12mo, 49.7% (95%CI: 38.9, 59.6; n=40). Six eyes were censored at 6mo due to loss of follow-up, and treatment succeeded on 40 eyes through the end of the follow-up period. Of the eyes in the failure group, the majority (41 eyes) met criteria for failure based on insufficient IOP reduction; two eyes underwent additional glaucoma surgery within one year of PCE/ECP surgery. Two

Cataract extraction and endoscopic cyclophotocoagulation

subjects met failure criteria based on both less than 20% reduction in IOP and an IOP ≥ 21 or ≤ 5 mm Hg at two consecutive visits. The corresponding Kaplan-Meier curve is shown in Figure 1.

Change in Intraocular Pressure Mean medicated IOP at baseline was 16.65 mm Hg. A statistically significant reduction in mean IOP from baseline was demonstrated at all follow-up time points, to 13.81 mm Hg (-17.06% change from baseline) at 1mo, 13.30 mm Hg (-19.56% change from baseline) at 3mo, 12.89 mm Hg (-22.56% change from baseline) at 6mo, and 13.38 mm Hg (-19.63% change from baseline) at 12mo. Figure 2 shows a comparison of IOP between the overall success and failure groups during the course of follow-up. The success group began at a significantly higher mean baseline IOP (19.6 mm Hg vs 14.0 mm Hg) and demonstrated a more pronounced decrease in IOP postoperatively. Mean IOP of the failure group did not change significantly from baseline at any follow-up time point.

Change in Medication Dependence The median number of glaucoma medications decreased from 2 at baseline to 1 at 12mo. Mean number of medications decreased significantly from 1.88 ± 1.07 at baseline to 1.36 ± 1.18 at 1mo, 1.17 ± 1.14 at 3mo, 1.36 ± 1.19 at 6mo, and 1.48 ± 1.27 at 12mo ($P < 0.001$ for all). These values are displayed over time in Figure 3. Figure 4 illustrates the change in number of subjects requiring a given number of medications before and after PCE/ECP surgery. Of the 9 patients who were not on medications prior to surgery, 4 were intolerant to topical medications, 3 did not want to initiate topical therapy, and 2 were noncompliant with medications.

Change in Visual Acuity Mean VA improved from a baseline value of 0.54 ± 0.6 logMAR to 0.33 ± 0.53 logMAR at 1mo, 0.38 ± 0.6 logMAR at 3mo, 0.36 ± 0.56 logMAR at 6mo, and 0.29 ± 0.48 logMAR at 12mo. The improvement in VA from baseline was statistically significant at all time points ($P < 0.001$).

DISCUSSION

This review of our experience with PCE/ECP surgery demonstrates the efficacy of this approach in the treatment of coexisting cataract and glaucoma. In our population consisting of patients with several forms of glaucoma, the procedure was moderately successful in reducing IOP by 20% or more. In fact, the procedure lowered IOP by an average of about 20% at 12mo, in addition to decreasing medication burden and improving VA. As is the case with other glaucoma treatments, patients with a higher preoperative IOP realized a significantly greater reduction in IOP and likelihood of success.

Traditional glaucoma filtration surgery has long been the standard for surgical management of glaucoma uncontrolled by medication or laser treatments. Despite the efficacy of

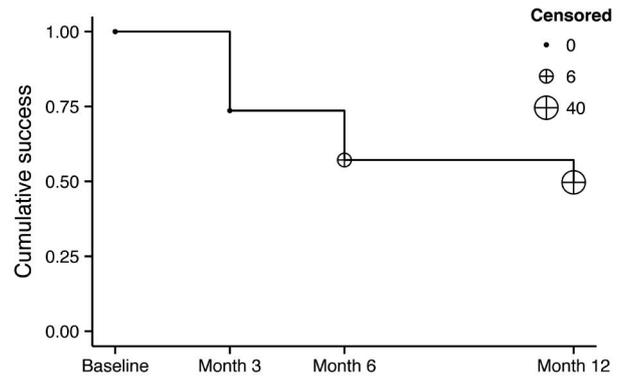


Figure 1 Kaplan-Meier curve for surgery success/failure.

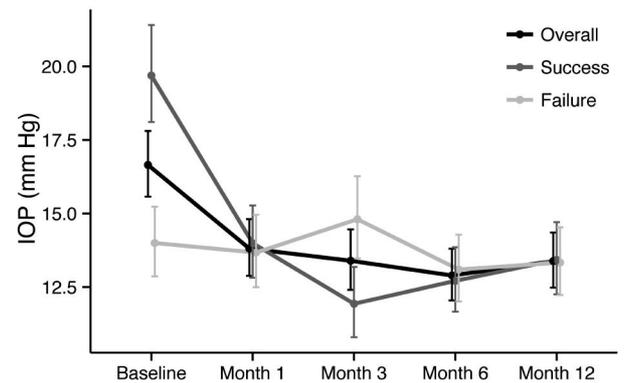


Figure 2 Observed means and confidence intervals for overall, surgery success, and surgery failure IOP by time point.

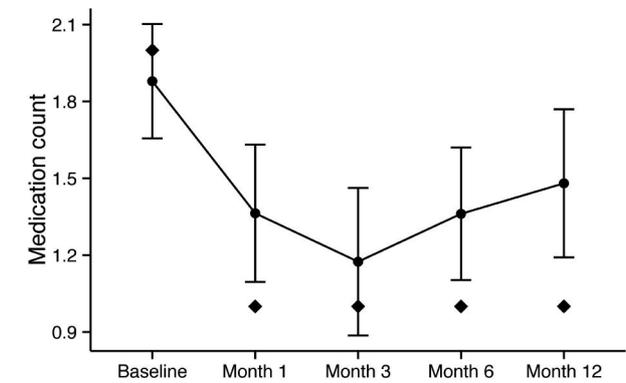


Figure 3 Mean medication count (point) by time point, with 95% CI and median (diamond).

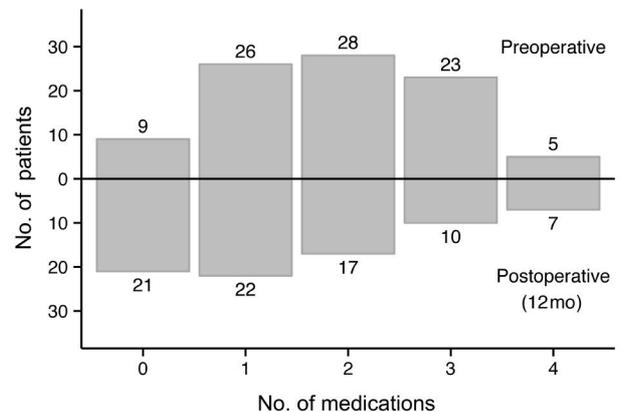


Figure 4 Comparison of preoperative and postoperative medication counts Preoperative: upward from X-axis; Postoperative: downward from X-axis.

filtration surgery, the potential for vision-threatening complications and prolonged patient recovery has led to a recent decline in popularity among surgeons. Minimally invasive procedures such as ECP, Trabectome (Neomedix, Tustin, CA, USA), and iStent (Glaukos, Laguna Hills, CA, USA) are now being employed earlier in the treatment of glaucoma in the hopes of avoiding the perils of traditional trabeculectomy and drainage device surgery. While these newer treatments have demonstrated excellent safety profiles, their efficacy in reducing IOP and medication dependence must be demonstrated to justify their utilization in the treatment paradigm.

Several recent studies have examined outcomes after PCE/ECP. The highest baseline IOP of any published series to date was reported in a Brazilian retrospective review examining 368 eyes, in which IOP decreased from 23.1 to 12.1 mm Hg at two years; medication use decreased from 1.4 to 0.4 medications and VA improved significantly [7]. Lindfield *et al* [8] published a retrospective case review of eyes with a variety of glaucoma subtypes treated with PCE/ECP which demonstrated a decrease in mean IOP from 21.5 to 14.4 mm Hg but no change in medication dependence at 2y post-operatively. A similarly structured study of eyes treated with PCE/ECP demonstrated a decrease in both IOP (21.1 to 16.1 mm Hg) and medication dependence (2.7 to 1.5 medications) at 12mo. The 12-month success rate was 55.5% using criteria similar to those used in our study [9]. A prospective, non-randomized, matched-control study by Francis *et al* [10] compared PCE/ECP to PCE alone in patients with medically controlled POAG. At 2y postoperatively, the PCE/ECP group showed a greater decrease in IOP (-2.1 *vs* -0.8 mm Hg at 2y) and medication dependence (0.4 *vs* 2.0 medications) than did the PCE alone group. Most recently, in a retrospective review by Siegel *et al* [11], PCE/ECP was compared to PCE alone in patients with a variety of glaucoma subtypes. Although IOP was reduced by a mean of 12.6% at 3y, this was not significantly different from the PCE alone group. However, mean medication dependence was significantly lower in the PCE/ECP group at final follow-up (0.2 *vs* 1.3). The full success rate ($\geq 20\%$ IOP reduction and ≥ 1 medication reduction) in the PCE/ECP group was 61.4% versus only 23.3% in the phaco alone group [11].

Our findings are largely consistent with previous studies on PCE/ECP. The reduction in IOP demonstrated in our study approximates that found in prior studies and supports a correlation between higher baseline IOP and a greater IOP reduction after surgery. The effect of PCE/ECP on medication dependence varies in the literature, from dramatic reduction [11] to no statistically significant change in medication reliance [8]. Our study demonstrates that a statistically significant reduction in medication use can be achieved after surgery. This reduction in medication use not

only decreases patient burden and cost but alleviates issues of compliance. Rates of treatment success are difficult to compare across studies due to differences in success criteria. Our criteria are modified from those outlined in the Tube Versus Trabeculectomy Study and thus do not consider medication use. Excluding medication dependence from our failure criteria precludes the capture of subjects who may have maintained their baseline IOP but still benefitted from PCE/ECP in terms of reduced medication burden. However, our failure criteria are intended to approximate those used in the glaucoma literature and are more specific to IOP effects. The study by Clement *et al* [9] uses similar success criteria to ours and reports a 12-month success rate of 55.7%, similar to our 12-month success rate of 49.7%.

The only predictive factor for success in our study was higher baseline IOP. Other patient or ocular factors were analysed but failed to show an association with treatment success including age, sex, race, prior glaucoma surgery, and medication use. Although there were no significant differences in success and failure rates between glaucoma sub-types, there was a trend for greater success in patients with chronic angle closure glaucoma (CACG). Future studies including more patients in this group are needed to better define the use of PCE/ECP in CACG. It should be noted that PCE alone can be effective in significantly lowering IOP in many patients with angle closure as well.

A few limitations to our study warrant consideration. Our study design was inherently limited by the lack of a formal control group undergoing PCE alone. The IOP-lowering effect of PCE alone has been documented in the literature and may account for a portion of the IOP reduction found in our study [19]. Our study population included patients with various glaucoma diagnoses and histories of prior glaucoma procedures; while this inclusive population may translate into greater generalizability of results, it renders the results less specific to a particular group. The small number of study patients with pigmentary glaucoma or pseudoexfoliative glaucoma should also be considered when applying our results to populations with these sub-types of glaucoma. Finally, our 12-month follow-up period was selected to allow for the inclusion of a greater number of subjects in our study, but this follow-up time frame limits conclusions about long-term outcomes.

In conclusion, our study shows that PCE/ECP surgery is a useful procedure for patients with coexisting cataract and glaucoma. The procedure demonstrates good IOP lowering efficacy as well as a reduction in medication burden and an improvement in visual acuity. The only predictive factor for success was a higher preoperative IOP. Large-scale prospective, randomized studies would be useful in further defining the efficacy and safety of PCE/ECP.

ACKNOWLEDGEMENTS

Foundation: Supported by the Slater Family Endowment (MYK) and NIH/NCATS Colorado CTSI Grant Number UL1 TR001082. Contents are the authors' sole responsibility and do not necessarily represent official NIH views.

Study concept and design: SooHoo JR, Seibold LK; Acquisition, analysis, and interpretation of data: Roberts SJ, SooHoo JR, Pantcheva MB, Kahook MY, Seibold LK; Drafting of the manuscript: Roberts SJ; Critical revision of the manuscript for important intellectual content: Seibold LK; Statistical analysis: Mulvahill M; Obtained funding: N/A; Study supervision: Seibold LK.

Conflicts of Interest: Roberts SJ, None; Mulvahill M, None; SooHoo JR, None; Pantcheva MB, None; Kahook MY, None; Seibold LK, None.

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